EXHIBIT Y

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DATE MAILED: 3-25-96

NOTICE OF ALLOWABILITY

PART I.

1. ☒ This communication is responsive to the interview of March 20, 1996
2. ☒ All the claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice Of Allowance And Issue Fee Due or other appropriate communication will be sent in due course.
3. ☒ The allowed claims are 65-68
4. ☐ The drawings filed on _____ are acceptable.
5. ☐ Acknowledgment is made of the claim for priority under 35 U.S.C. 119. The certified copy has [_] been received. [_] not been received. [_] been filed in parent application Serial No. _____, filed on _____
6. ☒ Note the attached Examiner's Amendment.
7. ☒ Note the attached Examiner Interview Summary Record, PTOL-413.
8. ☐ Note the attached Examiner's Statement of Reasons for Allowance.
9. ☒ Note the attached NOTICE OF REFERENCES CITED, PTO-892.
10. ☐ Note the attached INFORMATION DISCLOSURE CITATION, PTO-1449.

PART II.

A SHORTENED STATUTORY PERIOD FOR RESPONSE to comply with the requirements noted below is set to EXPIRE THREE MONTHS FROM THE "DATE MAILED" indicated on this form. Failure to timely comply will result in the ABANDONMENT of this application. Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

1. ☐ Note the attached EXAMINER'S AMENDMENT or NOTICE OF INFORMAL APPLICATION, PTO-152, which discloses that the oath or declaration is deficient. A SUBSTITUTE OATH OR DECLARATION IS REQUIRED.
2. ☒ APPLICANT MUST MAKE THE DRAWING CHANGES INDICATED BELOW IN THE MANNER SET FORTH ON THE REVERSE SIDE OF THIS PAPER.
   a. ☒ Drawing informalities are indicated on the NOTICE RE PATENT DRAWINGS, PTO-948, attached hereto or to Paper No. 4, CORRECTION IS REQUIRED.
   b. ☐ The proposed drawing correction filed on _____ has been approved by the examiner. CORRECTION IS REQUIRED.
   c. ☐ Approved drawing corrections are described by the examiner in the attached EXAMINER'S AMENDMENT. CORRECTION IS REQUIRED.
   d. ☐ Formal drawings are now REQUIRED.

Any response to this letter should include in the upper right hand corner, the following information from the NOTICE OF ALLOWANCE AND ISSUE FEE DUE: ISSUE BATCH NUMBER, DATE OF THE NOTICE OF ALLOWANCE, AND SERIAL NUMBER.

Attachments:

- ✓ Examiner's Amendment
- ✓ Examiner Interview Summary Record, PTOL-413
- _ Reasons for Allowance
- ✓ Notice of References Cited, PTO-892
- _ Information Disclosure Citation, PTO-1449
- _ Notice of Informal Application, PTO-152
- _ Notice re Patent Drawings, PTO-948
- _ Listing of Bonded Draftsmen
- _ Other

An Examiner's Amendment to the record appears below. Should the changes and/or additions be unacceptable to applicant, an amendment may be filed as provided by 37 C.F.R. § 1.312. To ensure consideration of such an amendment, it **MUST** be submitted no later than the payment of the Issue Fee.

Claims 1-64 and 69-73 were cancelled without prejudice.

In claim 65, lines 5-9 were deleted in their entirety and replaced with the following:

----(b) providing a wafer comprising on its surface a plurality of probe arrays, each probe array comprising a collection of probes, at least two of which are different, arranged in a spacially defined and physically addressable manner;---

(c) attaching the wafer to the body so that the probe arrays are exposed to the spaces of the wells.---

In claim 67, lines 2-3, the language "having a plurality of probe arrays" was deleted and replaced with the following: ---comprising on its surface a plurality of probe arrays, each probe array comprising a collection of probes, at least two of which are different, arranged in a spacially defined and physically addressable manner---

In the title, after "FOR", ---MAKING A DEVICE FOR--- was inserted.

Authorization for this Examiner's Amendment was given in a telephone interview with John Storella on March 20, 1996.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Paul Prebilic whose telephone number is (703) 308-2905. The examiner normally be reached on Monday-Thursday from 6:30 AM to 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Randall Green, can be reached on (703) 308-2912. The fax phone number for this Group is (703) 305-3590.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0858.

Paul Prebilic
Primary Examiner
Art Unit 3308

EXHIBIT Z

Webster's Third New International Dictionary

OF THE ENGLISH LANGUAGE UNABRIDGED

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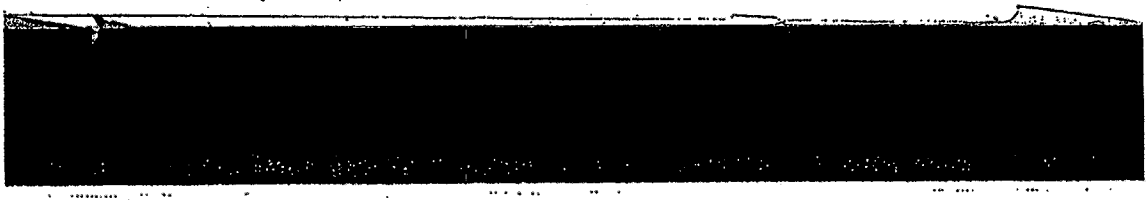


arnatta or **arnatto** var of ANNATTO

ar·naut \'är,naůt, ə'n-\ n -s usu cap [Turk arnavut Albanian, perh. fr. MGk Arbanitēs, alter. of Albanitēs, fr. Albania (fr. ML) + Gk -itēs -ite] : an inhabitant of Albania and neighboring mountainous regions; esp : an Albanian serving in the Turkish army

ar·ne·bia \är'nēbēə, ,ärnə'bēə\ n, cap [NL, fr. Ar arnabiyah] : a genus of Asiatic and northern African herbs (family Boraginaceae) having alternate leaves and yellow or violet flowers that change color in age — see PROPHET FLOWER

ar·nee \'är,nē\ n -s [Hindi arnī, fem. of arnā — more at ARNA] : ARNA; esp : the female arna

ar·neth index \'är,net-, -ed-\ n, cap A [after Joseph Arneth †1955 Ger. physician] : an age classification of blood granulocytes, specif. neutrophils, based on the number of lobes of the nucleus, increasing lobulation being regarded as a criterion of increasing age — compare SCHILLING INDEX, SHIFT TO THE LEFT, SHIFT TO THE RIGHT

arn·hem \'ärnəm, -n,hem\ adj, usu cap [fr. Arnhem, Netherlands] : of or from Arnhem, Netherlands : of the kind or style prevalent in Arnhem

ar·ni·ca \'ärnikə, -nē-, dial -nokē\ n [NL]. 1 a cap : a large genus of herbs (family Compositae) of the northern hemisphere having opposite leaves and flower heads that are discoid or have bright yellow rays — see LEOPARD'S BANE 2 . b -s : a plant of the genus Arnica 2 -s a : the dried flower head of an herb (Arnica montana) and other plants of the genus Arnica used for stimulant and local irritant effect esp. in the form of the tincture as an embrocation for bruises, sprains, and swellings b : the tincture made from arnica

arnica bud n [arnica, fr. the appearance of its leaves] : DANDELION

ar·nim·ite \'ärnə,mīt\ n -s [G arnimit, fr. von Arnim, name of the German family owning a mine near Planitz, Germany, its locality + G -it -ite] : a mineral $Cu_5(SO_4)_2(OH)_6.3H_2O$ consisting of a basic copper carbonate

ar·nold·ist \'ärn°ldəst\ n -s cap [Arnold of Brescia (Arnaldo da Brescia) †1155 Ital. political reformer + E -ist] : one of the followers of Arnold of Brescia, who preached against clerical riches and corruption and instigated the Romans to rebel against the temporal power of the pope

ar·nold's ganglion \'ärn°ld(z)-\ n, usu cap A [after Friedrich Arnold †1890 Ger. anatomist] : OTIC GANGLION

ar·nold sterilizer \-n°l(d)'st-\ n, usu cap A [after Julius Arnold †1915 Ger. pathologist] : a sterilizer used for fractional sterilization at 212°F by the free circulation of steam at atmospheric pressure

arnotta or **arnotto** var of ANNATTO

aroaco cap, var of ARHUACO

aroar \ə'-\ adj [a- + roar, v.] : ROARING

aroba var of ARABA

aro·ei·ra \,arə'wērə\ n -s [Pg] : any of several So. American resin-yielding timber trees of the genera Schinus and Astronium of the family Anacardiaceae

ar·oid \'a(ə)r,ȯid\ or **aroi·de·ous** \(')a,rȯidēəs, ə'rȯid-\ adj [aroid fr. NL Arum + E -oid; aroideous fr. aroid + -ous] : belonging to the family Araceae : ARACEOUS

aroid \"\ n -s : a plant of the family Araceae

aroint \ə'rȯint\ vb [origin unknown] v imper : BEGONE — used with reflexive thee (~ thee, witch —Shak.) ~ vt -ED/-ING/-S : to drive away by or as if by an exclamation or curse (the ... church duly ~ed witches —D.C.Peattie)

aro·li·um \ə'rōlēəm\ n, pl **aro·lia** \-lēə\ [NL, fr. ML, roll of cloth] : a padlike lobe projecting between the tarsal claws of many insects

arol·la \ə'rälə, -ōlə, -ōlə\ or **arolla pine** n -s [F dial. (Valais canton, Switzerland) arolla, prob. of non-IE origin; akin to G dial. (Switzerland) arve Swiss pine] : SWISS PINE

¹aro·ma \ə'rōmə\ n -s [alter. (influenced by L aroma) of earlier aromat, fr. ME, fr. OF, fr. L aromat-, aroma, fr. Gk arōmat-, arōma] 1 obs : SPICE — usu. used in pl. 2 a (1) : a distinctive pleasing odor : FRAGRANCE (the ~ of fresh coffee) (the ~ of a wood fire) (2) : the fragrance of a wine derived from the particular variety of grape used : BOUQUET b : any smell or odor (the gruesomely strong ~ of the old dog —Christopher Morley) 3 : a distinctive pervasive quality, characteristic, or atmosphere : FLAVOR (ancient capitals around which hang an ~ and mystery —Lin Yutang) (the ~ and fragrance of new thought, were perceptible —Nathaniel Hawthorne) syn see SMELL

²aroma \"\ or **aro·me** \-(,)mə\ n -s [AmerSp, fr. Sp aroma flower of the huisache, lit., fragrant plant product, fr. L, spice] : any of several spiny shrubs and trees (as the huisache)

aro·ma·den·drene \ə,rōmə'den,drēn\ n -s [ISV aroma + dendr- + -ene] : a sesquiterpenoid hydrocarbon $C_{15}H_{24}$ occurring as a major constituent of oils from several eucalyptus trees

aro·mal \ə'rōməl\ adj [aroma + -al] : AROMATIC

¹ar·o·mat·ic \,arə'madik, -atik, -ēk also ,er-\ adj [ME aromatyk, fr. MF aromatique, fr. LL aromaticus, fr. Gk arōmatikos, fr. arōmat-, arōma + -ikos -ic] 1 a : of, relating to, or having aroma: a : having a distinctive pleasing odor : sweet-smelling : FRAGRANT (the ~ breath of spruce and pine —Willa Cather) (an ~ blend of domestic and imported tobaccos) b : having a strong smell or odor (steerage accommodations ... were at best congested and strikingly ~ —Robert Rice) c : having a distinctive pervasive quality or atmosphere (all the places with ~ names —John Woodburn) 2 a : of, relating to, or characterized by the presence of at least one benzene ring — used of a large class of monocyclic, bicyclic, and polycyclic hydrocarbons and their derivatives (as benzene, toluene, naphthalene, phenol, aniline, salicylic acid); distinguished from alicyclic, aliphatic, heterocyclic; see CARBOCYCLIC; compare BENZENOID b : similar in chemical properties to the benzene ring or to compounds containing it — used esp. in relation to some unsaturated heterocyclic compounds (as thiophene and pyridine) — **ar·o·mat·i·cal·ly** \-ək(ə)lē, -ēk-, -li\ adv — **ar·o·mat·ic·ness** \-iknəs, -ēk-\ n -es

²aromatic \"\ n -s 1 : a plant, drug, or medicine characterized by a fragrant smell and usu. by a warm pungent taste (as ginger, cinnamon, and spices) 2 : an organic compound of the aromatic class

aromatical [aromatic + -al] archaic var of AROMATIC

aromatic bitters n pl : bitters that contain aromatic oils but little tannin

ar·o·ma·tic·i·ty \,arəmə'tisəd-ē, ə,rōm-\ n -es 1 : aromatic quality 2 : the quality of being or resembling a member of the aromatic class of chemical compounds

aromatic spirit of ammonia : a solution of ammonia and ammonium carbonate in alcohol and distilled water perfumed with the oils of lemon, lavender, and nutmeg and used as a stimulant, carminative, and antacid

aromatic sulfuric acid n : a mixture of sulfuric acid, tincture of ginger, oil or spirit of cinnamon, and alcohol formerly used as a tonic and astringent

aromatic vinegar n : a solution of acetic acid highly flavored with fragrant substances and used as smelling salts

aromatic water n : a saturated aqueous solution of a volatile oil or other volatile substance prepared either by distillation or by dissolving the substance

aromatic wintergreen n : WINTERGREEN 2a

aro·ma·ti·tes \ə,rōmə'tīd-ēz\ n, pl **aromati·tes** \-,tēz\ [L, fr. Gk arōmatitēs, fr. arōmatitēs aromatic, fr. arōmat-, arōma + -itēs -ite — more at AROMA] : a precious stone of ancient Arabia and Egypt

aro·ma·ti·za·tion \ə,rōməd-ə'zāshən, -mədə-, -mə,tī'z-\ n -s 1 : the act or process of making aromatic or the quality or state of being aromatic 2 a : chemical conversion into one or more aromatic compounds b in petroleum refining : conversion of aliphatic or alicyclic hydrocarbons into aromatic hydrocarbons by cyclization or dehydrogenation or both (as heptane into toluene or cyclohexane into benzene) — see HYDROFORMING

aro·ma·tize \ə'rōmə,tīz\ vt -ED/-ING/-S [ME aromatiser, fr. LL aromatizare, fr. Gk arōmatizein, fr. arōmat-, arōma + -izein -ize] 1 : to make aromatic (as with herbs) : give a fragrant scent to : FLAVOR 2 : to subject to chemical aromatization

arome var of AROMA

ar·o·mor·pho·sis \,arə'mȯrfəsəs sometimes -,mȯr'fō-\ n, pl **aromorpho·ses** \-,sēz\ [NL, fr. aro- (fr. Gk ara, or there and then, straightway; also, interrogative and connective particle) + morphosis; akin to Lith ir and, also, -er, interrogative particle] : biological evolution marked by general increase in the degree of organization without sharp specialization — compare ALLOMORPHOSIS

aro·nia \ə'rōnēə\ n, cap [NL, fr. Gk arōnia medlar tree] : a small genus of shrubs (family Rosaceae) comprising the chokeberries and having white or pink flowers in terminal compound cymes

aroon \ə'rün\ n -s [IrGael a rūn oh darling, fr. a oh + rūn darling, lit., secret, fr. OIr — more at RUNE] Irish : DARLING

arooshα var of ARUSHA

aro·ra \ə'rȯrə\ n pl, usu cap [native name in India] : a prosperous mercantile caste of Hindus of the Punjab region of the Indian subcontinent

arose past of ARISE

¹around \ə'raůnd\ adv [ME, prob. fr. ¹a- + round, n.] 1 a : in a circle or in circumference : ROUND (the wheel kept going ~) (the track is a mile ~) b : in a course making a circle or part of a circle (waltz your partner ~ again) (the wind has gone ~ to the south) c : by a circuitous route : in a roundabout way (the road goes ~ by the lake) 2 a : on every side : in all or various directions from a fixed point (the water of this well is famous for miles ~) b : in close from all sides so as to surround, confine, or envelop : close about (the old house is hemmed ~ by new apartments) (people crowded ~ to look at the wreck) c : in or near one's present situation (you have time to stay ~ a while) 3 a : here and there at random : at, in, or to various places : from one place to another : all about (for a year he traveled ~ from state to state) (the news got ~) b : to a particular place either specified or understood (invited him to come ~ for supper) c : into a situation permitting doing or attending — used with to (it was a long time before he got ~ to reading the book) (we'll get ~ to the work in the morning) 4 a : in rotation or succession : in turn (another winter has come ~) (he passed the candy ~ to his guests) b : from beginning to end : THROUGH (the region has a mild climate the year ~) c : in order (the other way ~) d : to a customary condition (as of health or consciousness) : to an improved state (medicines that will bring the invalids ~) 5 : somewhere close by : in the vicinity or neighborhood of : NEARBY (all he could do was stand ~ and wait) 6 a : in the reverse or opposite direction : to the rear (suddenly he turned ~) b : from one opinion, belief, or point of view to another : to an altogether different position or attitude (the public's reaction soon brought the legislators ~) 7 : in the neighborhood of : APPROXIMATELY, ABOUT (the book runs to ~ 300 pages) (he comes at ~ the same time every day) — been around : undergone many varied experiences : become worldly-wise or sophisticated (what most of them need is just a little advice from somebody who's been around —W.L. Gresham)

²around \"\ prep [ME, fr. around, adv.] 1 a : along the outer edge or boundary of : on all sides of (a neat yard with a fence ~ it) : so as to encircle or enclose : ABOUT (threw her arm ~ his neck) (several people seated ~ the table) b : so as to make the circuit of (~ the world in 80 days) or partial circuit of (a voyage ~ Cape Horn) : so as to follow the curving course of (coming ~ the bend of the river) c : so as to avoid or get past (leaping over fences and dodging ~ boulders) 2 a : in the neighborhood of : NEAR (the fields ~ the village) : in the same region with (the country ~ the source of the Nile) b : close to (only the men ~ the president knew of his illness) 3 a : in all directions outward from (stood looking ~ him) b : so as to have a center or basis in (primitive societies which are organized ~ kinship ties —Weston La Barre) 4 a : here and there at random in or throughout : ABOUT, OVER (constantly traveling ~ the country) b : from one part to another of (wandering restlessly ~ the house)

³around \"\ adj [¹around] 1 : going or moving about : ASTIR (he has been up and ~ for two days) 2 : in existence : ALIVE, LIVING, PRESENT (one of the most alertly intelligent of the artists ~ today —R.M.Coates) (the troubles arising out of lack of money have been ~ for a long time —Murray Illson)

around-the-clock \ə¦---¦-\ adj : being in effect, continuing, or lasting 24 hours a day : UNCEASING, CONSTANT (an around-the-clock operation)

arou·ra or **arura** \ə'rürə\ n, pl **arouras** or **aruras** \-rəz\ [Gk aroura, lit., tilled or arable land, fr. aroun to plow — more at EAR (to plow)] : an ancient Egyptian unit of land measure equal to 0.677 acres (27.4 ares)

arous·al \ə'raůzəl\ n -s : the act of arousing : the state of being aroused

arouse \ə'raůz\ vb -ED/-ING/-S [a- (perfective prefix) + rouse — more at ABEAR] vt 1 a : to awake from or as if from sleep : wake up (ran to the flaming house and aroused the old man) b : to rouse to action or readiness for action from a state of inactivity (the new force stirred and aroused the people — Sherwood Anderson) 2 : to give rise to : EXCITE, STIMULATE : stir into activity (the book and the play ... aroused debate within the party —E.W.Baldwin) ~ vi : to awake from or as if from sleep : rise (a soldier would ~ and turn his body to a new position —Stephen Crane) syn see STIR

arous·er \-zə(r)\ n -s : one that arouses

a ro·ve·scio \,ä,rō've(,)shō, -eshē,ō\ adv or adj [It a rovescio, a rovescio] also **al rovescio** \,äl-\ : upside down : backwards : in contrary motion — used as a direction in music indicating imitation by reversion or by inversion

arow \ə'rō\ adv (or adj) [ME arewe, arowe, fr. ¹a- + rewe, rowe row, line — more at ROW] : in a row, line, or rank

aroxy \(')a¦räksē\ adj [aroxy-, fr. aryl + oxy-] : ARYLOXY

ar·roy \ə'rȯi\ [aromatic + -yl] : an aromatic acid radical (as benzoyl)

ARP abbr air raid precautions

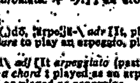
ar·peg·gian·do \(,)är,pejē'än(,)dō, ärpeˈj-\ adv [It, playing an arpeggio, verbal of arpeggiare to play an arpeggio, play on the harp] : in arpeggio

ar·peg·gi·at·ed \är'pejē,ādəd\ adj [It arpeggiato (past part. of arpeggiare) + E -ed] 1 of a chord : played as an arpeggio 2 of a passage : consisting of or played as arpeggios

ar·peg·gi·a·tion \(,)är,pejē'āshən\ n -s : arpeggio playing or writing

ar·peg·gi·a·to \(,)är,pejē'ä(,)tō, ärpeˈj-\ adj [It] : in arpeggios : ARPEGGIATED

ar·peg·gio \är'pej(ē,)ō, -e(,)jō\ n, pl **arpeggios** \-ōz\ or **arpeg·gi** \-e(,)jē\ [It, fr. arpeggiare to play on the harp, fr. arpa harp, of Gmc origin; akin to OHG harpha harp — more at HARP] 1 production of the tones of a chord in succession and not simultaneously 2 : a chord played in arpeggio



arpeggio 2

ar·peg·gioed \-ōd\ adj : ARPEGGIATED

ar·peg·gi·o·ne \(,)är,pejē'ō,nā\ n -s [It, fr. arpeggio] : a cellolike bowed instrument of the early 19th century having frets and drone strings

ar·pent \'ärpənt, -,pänt\ also **ar·pen** \-,pen, -pəⁿ\ n -s [MF arpent, fr. (assumed) VL arependis, prob. alter. of L arepennis, fr. Gaulish; akin to MIr airchenn, a measure of land area; both fr. a prehistoric Celtic compound whose first and second constituents respectively are akin to Gaulish are by, in front of (akin to OHG furi for, in front of) and to OIr cenn head, end, W pen — more at FOR] 1 : any of various old French units of land area; esp : a unit still used in certain French sections of Canada and the U.S. equal to about 0.85 acre 2 : a unit of length equal to one side of a square constituting one arpent

ar·que·bus var of HARQUEBUS

ar·que·rite \'ärkə,rīt\ n -s [F arquérite, fr. Arqueros, Chile, its locality + F -ite] : a mineral consisting of a soft malleable variety of amalgam

arr \'är, 'ärr\ n -s [ME arre, arre, of Scand origin; akin to ON err, ǫrr scar, OSw ar, ær, Dan ar, arr; akin to MLG are scar, G dial. arbe, Skt aru wound and perh. to ON rögg long hair, long wool — more at RUG] now dial Brit : SCAR

arr abbr 1 arranged; arrangement 2 arrival; arrive

ARR abbr [L anno regni regis or reginae] in the year of the king's or queen's reign

ar·ra·ca·cha \,arə'kachə, ,ärə'k-, ˈ- -\ also **ar·ra·cach** \-,kach, ˈ- -\ n, pl **arracachas** also **arracachas** [Sp arracacha, aracacha, fr. Quechua rakkácha] : a tropical American perennial herb (Arracacia xanthorrhiza or A. esculenta) that is related to the carrot and is cultivated in the uplands of northern and western So. America for its edible root — called also apio, Peruvian carrot

ar·ra·ca·cia \,arə'kāsh(ē)ə\ n, cap [NL, fr. Sp arracacha] : a genus of chiefly Mexican herbs (family Umbelliferae) having compound leaves, white flowers in umbels without an involucre, and a distinct stylopodium — see ARRACACHA

arrack also **ar·ak** or **ar·rak** \'arək, 'a,rak\ n -s [Ar 'araq sweet juice, liquor] : an alcoholic beverage from the Far East or Near East; esp : a liquor of high alcoholic content resembling rum in taste and distilled in the Far East from the fermented juice of the coconut palm or from a fermented mash of rice and molasses

arrack punch or **arrack punch** n [Sw arrakpunsch, fr. arrak arrack (fr. E arrack) + punsch punch, fr. E punch — more at PUNCH] : SWEDISH PUNSCH

ar·rah \'arə\ interj [IrGael ara] Irish — used to express surprise or excitement

¹ar·raign \ə'rān also a'-\ vt -ED/-ING/-S [ME arreinen, fr. MF araisnier to speak to, arraign, fr. OF, fr. a- (fr. L ad-) + raisnier to speak, fr. (assumed) VL rationare, fr. L ration-, ratio reason, reasoning — more at REASON] 1 : to call (a prisoner) to the bar of a court to answer to the charge of an indictment : ACCUSE, CHARGE 2 : to accuse of wrong, inadequacy, or imperfection : find fault with : DENOUNCE (St. Peter Damiani ... ~s the monks for teaching grammar rather than things spiritual —H.O.Taylor) syn see ACCUSE

²arraign \"\ vt -ED/-ING/-S [AF arainer, alter. of arramer, irreg. fr. ML adhramire, arramire to promise to perform a juridical act, to arraign, fr. L ad- + ML hramire, of Gmc origin; akin to OE hremman to hinder, ON kremma to clutch, Goth hramjan to crucify; akin to Russ kromy (pl.) loom] : to appeal to : DEMAND

ar·raign·er \-nə(r)\ n -s : one that arraigns

ar·raign·ment \-nmənt\ n -s [ME arreinement, fr. MF arainement, fr. OF, fr. araisnier + -ment] : the act of arraigning or the state of being arraigned : ACCUSATION, DENUNCIATION (the wholesale ~ of existing educational standards —F.N.Robinson)

arrame \ə'rām\ vt -ED/-ING/-S [ML arramire to arraign (as in arramire assisam to hold an assize) — more at ARRAIGN] law : COMMENCE (~ the assize)

arrand var of ARAIN

ar·range \ə'rānj also a'-\ vb -ED/-ING/-S [ME arengen, arengen, fr. MF arangier, arengier, fr. OF, fr. a- (fr. L ad-) + rengier to set in a row — more at RANGE] vt 1 : to put in correct, convenient, or desired order : adjust properly : DISPOSE, PLACE (the girl carefully arranged her hair) (minerals arranged according to the Dana classification) 2 : to put in order beforehand : make preparations for : PLAN (would be grateful to them for arranging her few remaining years —Victoria Sackville-West) 3 : to effect usu. by consulting : come to an agreement or understanding about : SETTLE (decided as a matter of wisdom to ~ a truce —C.B.Hitchcock) (the date of the marriage was finally arranged) 4 a : to adapt (a musical composition) by rescoring to voices or instruments other than those for which orig. written b : ORCHESTRATE (~ a folk melody) ~ vi 1 : to come to an agreement, understanding, or settlement (arranged with the travel agent for a June passage) 2 : to make preparations : PLAN (the band arranged for a series of concerts) syn see ORDER

ar·range·ment \-jmənt\ n -s [F, fr. MF arengement, fr. arengier + -ment] 1 a : the act or action of arranging or putting in correct, convenient, or desired order (there was time only for the quickest ~ of mind —Jane Austen) b : the quality or state of being arranged or put in order 2 : the style, manner, or way in which things are arranged : ORDER, SYSTEM (was shocked at the helter-skelter ~ of the papers —Jean Stafford) 3 : a preliminary step or measure : PREPARATION, PLAN — usu. used in pl. (when the emigration to America was decided upon, he was one of four to complete the ~s —R.G.Usher) 4 a : a structure or combination of things arranged in a particular way or for a specific purpose : COMBINATION (this does not prevent his paintings from being handsome aesthetic ~s —Encounter) (the church was decorated with ~s of roses and snapdragons) b : CONTRIVANCE, AFFAIR, THING (the machine was powered by a man who pumped a bicycle ~) 5 a : adaptation by rescoring of a musical composition to voices or instruments for which it was not orig. written b : a piece so adapted (an orchestral ~ of a song) 6 a : a settlement or adjustment esp. of a dispute or claim (I'm in a very delicate position but I'll fall in with any ~ Thespis may propose —W.S.Gilbert) b (1) : a mutual agreement or understanding (as between persons or nations) (nothing ... precludes the existence of regional ~s or agencies —Vera M. Dean) (2) : an agreement between a debtor and his creditors modifying his obligations to them 7 : PERMUTATION 3

ar·rang·er \-jə(r)\ n -s 1 : one that arranges 2 : one that transcribes music for voices or instruments for which it was not orig. written or adapts it to a style suitable to a particular group of performers — called also adapter

ar·rant \'arənt also 'er-\ adj [alter. of errant] 1 : wandering or roving about : ITINERANT, VAGRANT (an ~ thief) 2 a : OUT-AND-OUT, THOROUGHGOING, CONFIRMED, EXTREME (~ individualists pursuing separate courses —C.M.Smith) (his own portion ... of the omniscience —C.E.Montague) b : notoriously or outstandingly bad : SHAMELESS (is an ~ coward and shows the white feather at the slightest display of pluck in his antagonist —John Burroughs) — **ar·rant·ly** adv

ar·ras \'arəs also 'er- sometimes -ras or -a(ə)s\ n, pl **arras** [ME, fr. Arras, city in northern France] 1 a : a high-warp tapestry of 14th and 15th century Flemish origin having rich pictorial designs and being used for wall hangings and curtains b : any tapestry of similar design 2 : a wall hanging or hanging screen of tapestry (behind the ~ I'll convey myself —Shak.)

²arras \"\ n, pl **arras** [Sp, fr. LL arrha, fr. L, pl. of arra earnest — more at EARNEST] Spanish law : a gift made by a husband to his wife upon marriage

ar·ra·sene \,arə'sēn, ˈ- -\ n -s [arras + -ene (as in damascene)] : a silk or wool embroidery cord resembling chenille

ar·ras·tra \ə'rastrə\ or **ar·ras·tre** \-strē\ or **arras·tra** \ə'rästrə\ n -s [modif. of MexSp arrastra, fr. Sp, haulage, dragging, fr. arrastrar to drag, fr. a- (fr. L ad-) + rastrar to drag, fr. rastro rake, harrow, fr. L rastrum rake — more at RASTER] : a crude drag-stone mill for pulverizing ores (as those containing free gold)

ar·ras·tre \ə'rastrē\ n -s [PhilSp, fr. Sp, haulage, dragging] 1 Philippines : the operation of receiving, conveying, and loading or unloading merchandise on piers or wharves 2 (Sp, lit., dragging) : the act or process of dragging a dead bull from the ring after a bullfight

ar·rau \'a,raů, ə'raů, ə'rä(ə)\ n -s [AmerSp & Pg, fr. Maipure arrau] : a large turtle (Podocnemis expansa) of the group Pleurodira found in the Amazon river and valued for its edible eggs and as a source of oil

arrawak usu cap, var of ARAWAK

¹ar·ray \ə'rā, a'-\ vt -ED/-ING/-S [ME arayen, arrayen, fr. OF areer, arayer, fr. (assumed) VL arredare to arrange, fr. L ad- + (assumed) VL redare to provide, of Gmc origin; akin to Goth garaiths arranged — more at READY] 1 a : to set or place in order : draw up : MARSHAL (dons to ~ his men at the town-ward wall —A.C.Whitehead) (served only to ~ public sentiment ... against the owners —W.J.Ghent) b : to set or set forth in order (as a jury) for the trial of a cause : call (as a jury) man by man 2 : to clothe or dress esp. in splendid or impressive attire : dress up : deck out : ADORN (did she not ~ herself in what seemed unbelievably beautiful clothes —Sherwood Anderson)

²array \"\ n -s [ME aray, arrey, fr. OF arrei, arroi, arroi order, arrangement, dress, fr. areer, arayer] 1 a : a regular and imposing grouping or arrangement : ORDER (tending to place the great geographical interests in hostile ~ —U.B.Phillips) b : military order (with horse and chariots ranked in loose ~ —John Milton) c (1) : an orderly listing of jurors impaneled (2) : JURY d : a group of individuals or kinds of individuals that has a definite modal point forming a center of variation (an interesting ~ of halophiles) 2 a : CLOTHING, ATTIRE

[redacted]

EXHIBIT AA

EXHIBIT REDACTED IN ITS ENTIRETY

EXHIBIT BB

Merriam-Webster's Collegiate® Dictionary

TENTH EDITION

Merriam-Webster, Incorporated
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house–train \'hau̇s-ˌtrān\ *vt* (1924) *chiefly Brit* : HOUSEBREAK

house·wares \'hau̇s-ˌwarz, -ˌwerz\ *n pl* (1921) : furnishings for a house; *esp* : small articles of household equipment (as cooking utensils or small appliances)

house·warm·ing \'hau̇s-ˌwȯr-miŋ\ *n* (1577) : a party to celebrate the taking possession of a house or premises

house·wife \'hau̇s-ˌwīf; *esp 2 & in early poetry* 'hə-zəf *or* -səf\ *n, pl* **house·wives** \'hau̇s-ˌwīvz *also* 'hau̇z-ˌwīvz; 'hə-zəfs, -zəvz, -səfs, -səvz\ (13c) **1** : a married woman in charge of a household **2** : a pocket-size container for small articles (as thread) — **house·wife·li·ness** \-lē-nəs\ *n* — **house·wife·ly** \-lē\ *adj* — **house·wif·ery** \-ˌwī-f(ə-)rē; *Brit* -(ˌ)wi-f(ə-)rē *also* 'hə-zə-frē\ *n* — **house·wif·ey** \'hau̇s-ˌwī-fē\ *adj*

house·work \'hau̇s-ˌwərk\ *n* (1841) : the work of housekeeping

1**hous·ing** \'hau̇-ziŋ\ *n* (14c) **1 a** : SHELTER, LODGING **b** : dwellings provided for people **2 a** : a niche for a sculpture **b** : the space taken out of a structural member (as a timber) to admit the insertion of part of another **3** : something that covers or protects: as **a** : a case or enclosure (as for a mechanical part or an instrument) **b** : a casing (as an enclosed bearing) in which a shaft revolves **c** : a support (as a frame) for mechanical parts

2**housing** *n* [ME, fr. *house* housing (fr. MF *houce,* of Gmc origin) + *-ing;* akin to MHG *hulft* covering] (15c) : CAPARISON 1

housing development *n* (1951) : a group of individual dwellings or apartment houses typically of similar design that are usu. built and sold or leased by one management

housing estate *n* (1920) *Brit* : HOUSING DEVELOPMENT

housing project *n* (ca. 1937) : a publicly supported and administered housing development planned usu. for low-income families

Hou·yhn·hnm \'hwi-nəm, hü-'i-nəm\ *n* : a member of a race of horses endowed with reason in Swift's *Gulliver's Travels*

hove *past and past part of* HEAVE

hov·el \'hə-vəl, 'hä-\ *n* [ME] (15c) **1** : an open shed or shelter **2** : TABERNACLE **3** : a small, wretched, and often dirty house : HUT

hov·er \'hə-vər, 'hä-\ *vi* **hov·ered; hov·er·ing** \-v(ə-)riŋ\ [ME *hoveren,* freq. of *hoven* to hover] (15c) **1 a** : to hang fluttering in the air or on the wing **b** : to remain suspended over a place or object **2 a** : to move to and fro near a place : fluctuate around a given point ⟨unemployment ~*ed* around 10%⟩ **b** : to be in a state of uncertainty, irresolution, or suspense — **hover** *n* — **hov·er·er** \-vər-ər\ *n*

hov·er·craft \-vər-ˌkraft\ *n* (1959) : a vehicle that is supported above the surface of land or water by a cushion of air produced by downwardly directed fans

1**how** \'hau̇\ *adv* [ME, fr. OE *hū;* akin to OHG *hwuo* how, OE *hwā* who — more at WHO] (bef. 12c) **1 a** : in what manner or way **b** : for what reason : WHY **c** : with what meaning : to what effect **d** : by what name or title ⟨~ art thou called —Shak.⟩ **2** : to what degree or extent **3** : in what state or condition ⟨~ are you⟩ **4** : at what price ⟨~ a score of ewes now —Shak.⟩ — **how about** : what do you say to or think of ⟨*how about* it, are you going?⟩ — **how come** : how does it happen that : WHY

2**how** *conj* (bef. 12c) **1 a** : the way or manner in which ⟨remember ~ they fought⟩; *also* : the state or condition in which **b** : THAT ⟨told them ~ he had a situation —Charles Dickens⟩ **2** : HOWEVER, AS ⟨a reader can shift his attention ~ he likes —William Empson⟩

3**how** \'hau̇\ *n* (1533) **1** : a question about manner or method **2** : MANNER, METHOD

1**how·be·it** \hau̇-'bē-ət\ *conj* (14c) : ALTHOUGH

2**howbeit** *adv* (15c) : NEVERTHELESS

how·dah \'hau̇-də\ *n* [Hindi *hauda,* fr. Ar *hawdaj*] (1774) : a seat or covered pavilion on the back of an elephant or camel

howdah

how·dy \'hau̇-dē\ *interj* [alter. of *how do ye*] (1712) — used to express greeting — **howdy** *vb*

howe \'hau̇, 'hō\ *n* [ME (northern) *holl* hollow place, fr. OE *hol,* fr. *hol,* adj., hollow — more at HOLE] (bef. 12c) *Scot* : HOLLOW, VALLEY

1**how·ev·er** \hau̇-'e-vər\ *conj* (14c) **1** : in whatever manner or way that ⟨will help ~ I can⟩ **2** *archaic* : ALTHOUGH

2**however** *adv* (14c) **1 a** : in whatever manner or way ⟨shall serve you, sir, truly, ~ else —Shak.⟩ **b** : to whatever degree or extent ⟨has done this for ~ many thousands of years —Emma Hawkridge⟩ **2** : in spite of that : on the other hand ⟨still seems possible, ~, that conditions will improve⟩ ⟨would like to go; ~, I think I'd better not⟩ **3** : how in the world ⟨~ did you manage to do it⟩

howff *or* **howf** \'hau̇f, 'hōf\ *n* [D *hof* enclosure; akin to OE *hof* enclosure, and perh. to *hufil* hill] (1711) *Scot* : HAUNT, RESORT

how·it·zer \'hau̇-ət-sər\ *n* [D *houwitser,* ultim. fr. Czech *houfnice* ballista] (1695) : a short cannon used to fire projectiles at medium muzzle velocities and with relatively high trajectories

howl \'hau̇(ə)l\ *vb* [ME *houlen;* akin to MHG *hiulen* to howl] *vi* (14c) **1** : to emit a loud sustained doleful sound characteristic of members of the dog family **2** : to cry out loudly and without restraint under strong impulse (as pain, grief, or amusement) **3** : to go on a spree or rampage ~ *vt* **1** : to utter with unrestrained outcry **2** : to drown out or cause to fail by adverse outcry — used esp. with *down* ⟨~*ed* down the speaker⟩ — **howl** *n*

howl·er \'hau̇-lər\ *n* (1800) **1 a** : one that howls **b** : HOWLER MONKEY **2** : a humorous and ridiculous blunder

howler monkey *n* (1932) : any of a genus (*Alouatta*) of So. and Central American monkeys that have a long prehensile tail and enlargement of the hyoid and laryngeal apparatus enabling them to make loud howling noises

howl·ing \'hau̇-liŋ\ *adj* (1599) **1** : producing or marked by a sound resembling a sustained howl ⟨a ~ storm⟩ **2** : DESOLATE, WILD ⟨a ~ wilderness⟩ **3** : very great : PRONOUNCED ⟨a ~ success⟩ — **howl·ing·ly** *adv*

how·so·ev·er \ˌhau̇-sə-'we-vər\ *adv* (14c) **1** : in whatever manner **2** : to whatever degree or extent

1**how–to** \'hau̇-'tü\ *adj* (1926) : giving practical instruction and advice (as on a craft) ⟨~ books on all sorts of hobbies —Harry Milt⟩

2**how–to** *n* (1954) : a practical method or instruction ⟨the ~*s* of balancing a checkbook⟩

1**hoy** \'hȯi\ *interj* [ME] (14c) — used in attracting attention or in driving animals

2**hoy** *n* [ME, fr. MD *hoei*] (15c) **1** : a small usu. sloop-rigged coasting ship **2** : a heavy barge for bulky cargo

hoya \'hȯi-(y)ə\ *n* [NL, fr. Thomas *Hoy* †1821 Eng. gardener] (1851) : any of a genus (*Hoya*) of climbing Asian and Australian evergreen shrubs of the milkweed family

hoy·den \'hȯi-dᵊn\ *n* [perh. fr. obs D *heiden* country lout, fr. MD, heathen; akin to OE *hǣthen* heathen] (1676) : a girl or woman of saucy, boisterous, or carefree behavior — **hoy·den·ish** \-ish\ *adj*

hoyle \'hȯi(ə)l\ *n, often cap* [Edmond *Hoyle* †1769 Eng. writer on games] (1906) : an encyclopedia of the rules of indoor games and esp. card games

Hsia \shē-'ä\ *n* [Chin (Beijing) *Xià*] (ca. 1909) : the legendary first dynasty of Chinese history traditionally dated from about 2200–1766 B.C.

HTLV \ˌāch-(ˌ)tē-(ˌ)el-'vē\ *n* [*h*uman *T*-cell *l*ymphotropic *v*irus] (1980) : any of several retroviruses — often used with a number or Roman numeral to indicate type

HTLV–III \-(ˌ)vē-'thrē\ *n* (1984) : HIV-1

hua·ra·che \wə-'rä-chē, hə-\ *n* [MexSp, fr. Tarascan *kʷarách̄i*] (1892) : a low-heeled sandal having an upper made of interwoven leather strips

hub \'həb\ *n* [prob. alter. of 2*hob*] (1649) **1** : the central part of a circular object (as a wheel or propeller) **2 a** : a center of activity : FOCAL POINT **b** : an airport or city through which an airline routes most of its traffic **3** : a steel punch from which a working die for a coin or medal is made

hub–and–spoke *adj* (1980) : being or relating to a system of routing air traffic in which a major airport serves as a central point for coordinating flights to and from other airports

Hub·bard squash \'hə-bərd-\ *n* [prob. fr. the name *Hubbard*] (1868) : any of various often large variably green winter squashes — called also *Hubbard*

hub·ble–bub·ble \'hə-bəl-ˌbə-bəl\ *n* [redupl. of *bubble*] (1634) **1** : WATER PIPE 2 **2** : a flurry of sound or activity : COMMOTION

hub·bub \'hə-ˌbəb\ *n* [perh. of Ir origin; akin to ScGael *ub ub,* interj. of contempt] (1555) **1** : NOISE, UPROAR **2** : CONFUSION, TURMOIL

hub·by \'hə-bē\ *n, pl* **hubbies** [by alter.] (1688) : HUSBAND

hub·cap \'həb-ˌkap\ *n* (1903) : a removable usu. metal cap over the end of an axle; *esp* : one used on the wheel of a motor vehicle

hu·bris \'hyü-brəs\ *n* [Gk *hybris*] (1884) : exaggerated pride or self-confidence — **hu·bris·tic** \hyü-'bris-tik\ *adj*

huck \'hək\ *n* (1851) : HUCKABACK

huck·a·back \'hə-kə-ˌbak\ *n* [origin unknown] (1690) : an absorbent durable fabric of cotton, linen, or both used chiefly for towels

huck·le·ber·ry \'hə-kəl-ˌber-ē\ *n* [perh. alter. of *hurtleberry* (huckleberry)] (1670) **1** : any of a genus (*Gaylussacia*) of American shrubs of the heath family; *also* : the edible dark blue to black usu. acid berry (esp. of *G. baccata*) with 10 nutlets **2** : BLUEBERRY

1**huck·ster** \'hək-stər\ *n* [ME *hukster,* fr. MD *hokester,* fr. *hoeken* to peddle] (13c) **1** : HAWKER, PEDDLER **2** : one who produces promotional material for commercial clients esp. for radio or television — **huck·ster·ism** \-stə-ˌri-zəm\ *n*

2**huckster** *vb* **huck·stered; huck·ster·ing** \-st(ə-)riŋ\ *vi* (1592) : HAGGLE ~ *vt* **1** : to deal in or bargain over **2** : to promote by showmanship

1**hud·dle** \'hə-dᵊl\ *vb* **hud·dled; hud·dling** \'həd-liŋ, 'hə-dᵊl-iŋ\ [prob. fr. or akin to ME *hoderen* to huddle] *vt* (1579) **1** *Brit* : to arrange carelessly or hurriedly **2 a** : to crowd together **b** : to draw (oneself) together : CROUCH **3** : to wrap closely in (as clothes) ~ *vi* **1 a** : to gather in a close-packed group **b** : to curl up : CROUCH **2 a** : to hold a consultation **b** : to gather in a huddle in football — **hud·dler** \'həd-lər, 'hə-dᵊl-ər\ *n*

2**huddle** *n* (1586) **1** : a close-packed group : BUNCH ⟨~*s* of children⟩ ⟨a ~ of cottages⟩ **2 a** : MEETING, CONFERENCE ⟨secret ~*s* were held by five leading Republicans —*Newsweek*⟩ **b** : a brief gathering of football players away from the line of scrimmage to receive instructions (as from the quarterback) for the next down

Hu·di·bras·tic \ˌhyü-də-'bras-tik\ *adj* [irreg. fr. *Hudibras,* satirical poem by Samuel Butler †1680] (1712) **1** : written in humorous octosyllabic couplets **2** : MOCK-HEROIC — **Hudibrastic** *n*

hue \'hyü\ *n* [ME *hewe,* fr. OE *hīw;* akin to ON *hȳ* plant down, Goth *hiwi* form] (bef. 12c) **1** : COMPLEXION, ASPECT ⟨political parties of every ~ —Louis Wasserman⟩ **2 a** : COLOR **b** : gradation of color **c** : the attribute of colors that permits them to be classed as red, yellow, green, blue, or an intermediate between any contiguous pair of these colors — compare BRIGHTNESS 2, LIGHTNESS 2, SATURATION 4

hue and cry *n* [*hue* (outcry)] (15c) **1 a** : a loud outcry formerly used in the pursuit of one who is suspected of a crime **b** : the pursuit of a suspect or a written proclamation for the capture of a suspect **2** : a clamor of alarm or protest **3** : HUBBUB

hued \'hyüd\ *adj* (bef. 12c) : COLORED — usu. used in combination ⟨green-*hued*⟩

1**huff** \'həf\ *vb* [imit.] *vi* (1583) **1** : to emit puffs (as of breath or steam) **2 a** : to make empty threats : BLUSTER **b** : to react or behave indignantly ⟨~*ed* off in anger⟩ ~ *vt* **1** : to puff up : INFLATE **2** *archaic* : to treat with contempt : BULLY **3** : to make angry **4** : to utter with indignation or scorn

2**huff** *n* (1599) : a usu. peevish and transitory spell of anger or resentment ⟨quit in a ~⟩ *syn* see OFFENSE

huff·ish \'hə-fish\ *adj* (ca. 1755) : ARROGANT, SULKY

huffy \'hə-fē\ *adj* **huff·i·er; -est** (1677) **1** : HAUGHTY, ARROGANT **2 a** : roused to indignation : IRRITATED **b** : easily offended : TOUCHY — **huff·i·ly** \'hə-fə-lē\ *adv* — **huff·i·ness** \-fē-nəs\ *n*

hug \'həg\ *vt* **hugged; hug·ging** [perh. of Scand origin; akin to ON

EXHIBIT CC

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1-17-02
Enter claims only
No marked up version (Specification)

Attorney Docket 1067.1B (A1-32US3)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Donald M. BESEMER et al.	Examiner:	J. Siew
U.S. Serial No.:	09/907,196	Art Unit:	1656
Filed:	July 17, 2001		
Title:	BIOARRAY CHIP REACTION APPARATUS AND ITS MANUFACTURE		

Commissioner for Patents
Washington, D.C. 20231

AMENDMENT

In response to the Office Action mailed October 12, 2001, please amend this application as follows:

In the Abstract:

Please enter the following new Abstract:

A package for hybridization includes a substrate and a housing. The substrate has a first surface that includes an array of probes having biological polymers immobilized thereon. The housing includes a fluid cavity constructed and arranged for hybridization of a target to a probe of the probe array located inside the fluid cavity. The housing also includes a bar code.

In the Specification:

On page 1, please delete lines 4-8 and replace with the following:

This application is a continuation of U.S. Application Ser. No. 09/302,052, filed on April 29, 1999, now U.S. Patent 6,287,850; which is a continuation of U.S. Application Ser. No. 08/485,452, filed on June 7, 1995, now U.S. Patent 5,945,334; which in turn is a continuation-in-part of U.S. Application Ser. No. 08/255,682 filed on June 8, 1994. Each of these applications is incorporated herein by reference in its entirety for all purposes.

On page 6 line 19, before "Fig. 1a" please enter the following:

U.S. Patent 5,143,854 describes an improved method and apparatus for the preparation of a variety of polymers. In one preferred embodiment described in U.S. Patent 5,143,854, linker molecules are provided on a substrate. A terminal end of the linker molecules is provided with a reactive functional group protected with a photoremovable protective group. Using lithographic methods, the

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photoremovable protective group is exposed to light and removed from the linker molecules in first selected regions. The substrate is then washed or otherwise contacted with a first monomer that reacts with exposed functional groups on the linker molecules. In a preferred embodiment, the monomer is an amino acid containing a photoremovable protective group at its amino or carboxy terminus and the linker molecule terminates in an amino or carboxy acid group bearing a photoremovable protective group.

A second set of selected regions is, thereafter, exposed to light and the photoremovable protective group on the linker molecule/protected amino acid is removed at the second set of regions. The substrate is then contacted with a second monomer containing a photoremovable protective group for reaction with exposed functional groups. This process is repeated to selectively apply monomers until polymers of a desired length and desired chemical sequence are obtained. Photolabile groups are then optionally removed and the sequence is, thereafter, optionally capped. Side chain protective groups, if present, are also removed.

By using the lithographic techniques disclosed herein, it is possible to direct light to relatively small and precisely known locations on the substrate. It is, therefore, possible to synthesize polymers of a known chemical sequence at known locations on the substrate.

The resulting substrate will have a variety of uses including, for example, screening large numbers of polymers for biological activity. To screen for biological activity, the substrate is exposed to one or more receptors such as antibodies, whole cells, receptors on vesicles, lipids, or any one of a variety of other receptors. The receptors are preferably labeled with, for example, a fluorescent marker, radioactive marker, or a labeled antibody reactive with the receptor. The location of the marker on the substrate is detected with, for example, photon detection or autoradiographic techniques. Through knowledge of the sequence of the material at the location where binding is detected, it is possible to quickly determine which sequence binds with the receptor and, therefore, the technique can be used to screen large numbers of peptides. Other possible applications of the inventions herein include diagnostics in which various antibodies for particular receptors would be placed on a substrate and, for example, blood sera would be screened for immune deficiencies.

As also described in U.S. Patent 5,143,854, the substrate, the area of synthesis, and the area for synthesis of each individual polymer could be of any size or shape. For example, squares, ellipsoids, rectangles, triangles, circles, or portions thereof, along with irregular geometric shapes, may be utilized. Duplicate synthesis areas may also be applied to a single substrate for purposes of redundancy.

In one embodiment the regions on the substrate will have a surface area of between about 1 cm^2 and 10^{-10} cm^2. In some embodiments these regions have areas of less than about 10^{-1} cm^2, 10^{-2} cm^2, 10^{-3} cm^2, 10^{-4} cm^2, 10^{-5} cm^2, 10^{-6} cm^2, 10^{-7} cm^2, 10^{-8} cm^2, or 10^{-10} cm^2. In a preferred embodiment, these regions are between about 10 x 10 μm and 500 x 100 μm.

In some embodiments a single substrate supports more than about 10 different monomer sequences and preferably more than about 100 different monomer sequences, although in some embodiments more than about 10^3, 10^4, 10^5, 10^6, 10^7, or 10^8 different sequences are provided on a substrate. Of course, within a region of the substrate in which a monomer sequence is synthesized, it is preferred that the monomer sequence be substantially pure. In some embodiments, regions of the substrate contain polymer sequences which are at least about 1%, 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 60%, 70%, 80%, 90%, 95%, 96%, 97%, 98%, or 99% pure.

According to some embodiments, several sequences are intentionally provided within a single region so as to provide an initial screening for biological activity, after which materials within regions exhibiting significant binding are further evaluated.

Please delete the text on page 22, lines 8 through 16, and replace it by entering the following:

Thereafter, the package may be aligned on a detection or imaging system, such as those disclosed in U.S. Pat. No. 5,143,854 (Pirrung et al.) or U.S. Patent No. 5,631,734, already incorporated herein by reference for all purposes. Such detection systems may take advantage of the package's asymmetry (i.e., non-flush edge) by employing a holder to match the shape of the package specifically. Thus, the package is assured of being properly oriented and aligned for scanning. The imaging systems are capable of qualitatively analyzing the reaction between the probes and targets. Based on this analysis, sequence information of the targets is extracted.

U.S. Patent 5,631,734 discloses a fluorescent detection device used to detect fluorescently labeled targets on a substrate. The substrate comprises a number of presynthesized probes on its surface. The substrate may be transparent to a wide spectrum of light. In some embodiments, the substrate is made of a conventional microscope glass slide or cover slip. It is preferable that the substrate be as thin as possible while still providing adequate physical support. Preferably, the substrate is less than about 1 mm thick, more preferably less than 0.5 mm thick. Typically the substrate is a microscope glass slide of about 0.7 mm or 700 μm thick. In alternative embodiments, the substrate may be made of quartz or silica. The substrate may be mounted on a flow cell. The flow cell includes a body having a cavity on a surface thereof. The cavity is between about 50 and 1500 μm deep with a preferred depth of 1000 μm. The bottom of the cavity is preferably light absorbing so as to prevent reflection of impinging light. When mounted to the flow cell, the substrate seals the cavity except for an inlet port and an outlet port.

The fluorescent detection device includes a light source that generates a beam of light to excite the fluorescein labeled targets in the flow cell. The light source may be a argon laser that generates a beam having a wavelength of about 488 nm, which in some embodiments may be a model 2017 or model 161C manufactured by Spectra-Physics. Other lasers, such as diode lasers, helium neon

lasers, dye lasers, titanium sapphire lasers, Nd:YAG lasers or others may also be employed. The laser is directed at the inner surface of the substrate through an optical train comprised of various optical elements described in detail in U.S. Patent 5,631,734.

In response to the excitation light, fluorescein labeled targets in the flow cell fluoresce light having a wavelength greater than about 520 nm. The fluorescence is collected by a microscope objective and passed to an optical lens. In practice, light collected by the microscope objective contains both fluorescence emitted by the fluorescein and 488 nm laser light reflected from the surface of the substrate inside the cell. Most of the fluorescent component passes through a dichroic mirror and is then focused by a lens through a confocal pinhole onto a photomultiplier tube for detecting the number of photons present therein. The confocal pinhole transmits florescence originating from the focal plane of the microscope objective and filters out light originating from other planes, such as from the glass or reagent inside the hybridization cell. Accordingly, the signal-to-noise ratio of the fluoresced light is increased. Additionally, a filter is preferably located between the photomultiplier tube and the confocal pinhole. The fluorescent detection device records a number of photons of the detected fluorescent light as a function of a substrate location.

In the Claims:

28. (Twice Amended) A package for hybridization, comprising:

a substrate comprising a first surface including a probe array with different probes comprising biological polymers immobilized on said first surface; said probe array including a density exceeding 100 different biological polymers per cm^2; and

a housing including a fluid cavity constructed and arranged for hybridization of a target to a probe of said probe array, said housing including a bar code.

29. (Amended) A package for hybridization, comprising:

an optically transparent chip comprising a first surface including an array of probes comprising biological polymers immobilized on said first surface; and

a housing including a fluid cavity constructed and arranged for hybridization of a target to a probe of said probe array located inside said fluid cavity, said housing including a bar code and being arranged for use with a detection system.

30. (Amended) The package of claim 29, wherein said detection system is constructed and arranged for scanning said probe array, said probe array being located inside said fluid cavity.

cnt C1

31. (Amended) The package of claim 29, wherein said housing includes an alignment structure arranged for alignment of said probe array with respect to said detection system.

32. (Amended) The package of claim 29, wherein said detection system is constructed to detect fluorescent light emitted from said array and transmitted through said optically transparent chip and outside said package, said detected fluorescent light being used to quantitatively analyze said hybridization between said probe and target.

33. (as filed) The package of claim 28, wherein said housing includes an alignment structure arranged for alignment of said probe array with respect to a detection system.

C2

34. (Amended) A probe array deposited on a substrate, comprising:

a probe array including different probes comprising biological polymers immobilized on said substrate and having a density exceeding 100 different biological polymers per cm^2, and

a bar code.

35. (Amended) The probe array of claim 34, wherein said bar code is located on a housing forming a package constructed to accommodate said substrate and including an alignment structure being arranged for use with a detection system.

36. (as filed) The probe array of claim 35, wherein said alignment structure is constructed to predefine a position of said probe array with respect to said detection system.

35 C

Please enter the following new claims:

37. A package for supporting a probe array, comprising:

an optically transparent chip comprising an array of different probes including biological polymers, immobilized on a surface of said chip;

a housing constructed to receive said chip; and

a bar code associated with said chip.

38. The package of claim of claim 37, wherein said housing including a cavity constructed to receive said array of probes enclosed therein.

39. The package of claim 38, wherein said housing includes an alignment structure arranged for use with a detection system.

40. The package of claim 39, wherein said detection system is constructed and arranged to scan said probe array located inside said housing.

41. The package of claim 38, wherein said detection system is constructed and arranged for scanning said probe array to quantitatively analyze hybridization between said probes and various targets.

42. The package of claim 41, wherein said housing is constructed for introduction of fluid to contact said probe array and to hybridize said probes to targets delivered by said fluid.

43. The package of claim 38, wherein said housing includes an alignment structure arranged for use with a detection system; said detection system being constructed to detect fluorescent light emitted from said array and transmitted through said chip.

44. The package of claim 28, 29, 35 or 37, wherein said biological polymers include nucleic acids.

45. The package of claim 44, wherein said nucleic acids are attached to said surface through a linker group.

46. The package of claim 45, wherein said nucleic acids are from 4 to 20 nucleotides in length.

47. The package of claim 28, 29, 35 or 37, wherein each of said polymers are separately located within an area of about 1 μm^2 to about 1000 μm^2.

48. The package of claim 47, wherein said nucleic acids have a density exceeding 400 different nucleic acids per cm^2.

49. The package of claim 47, wherein said nucleic acids have a density exceeding 1000 different nucleic acids per cm^2.

50. The package of claim 28, 29, 35 or 37, wherein said biological polymers are attached to said substrate by selectively illuminating said substrate.

51. The package of claim 28, 29, 35 or 37, wherein said biological polymers include oligonucleotides.

52. The package of claim 28, 29, 35 or 37, wherein said biological polymers include proteins or polypeptides.

58. The package of claim 28, 29, 35 or 37, wherein said biological polymers include one of the following: agonists and antagonists for cell membrane receptor, toxins, venoms, viral epitopes, hormones, hormone receptors, enzymes, enzyme

substrates, cofactors, drugs, lectins, sugars, oligosaccharides, and monoclonal antibodies.

54. The package of claim 28, wherein said nucleic acids have a density exceeding 400 different nucleic acids per cm^2.

55. The package of claim 28, wherein said nucleic acids have a density exceeding 1000 different nucleic acids per cm^2.

56. The package of claim 37 wherein said biological polymers are in fluid communication.

57. The package of claim 37 wherein said biological polymers are separately located within an area of less than 10^{-2} cm^2.

58. The package of claim 37 wherein there are more than 100 different sequences in the array.

59. The package of claim 37 wherein there are more than 1000 different sequences in the array.

60. The package of claim 28, 29 or 37 wherein said biological polymers are covalently attached to said surface.

61. The array of claim 34 wherein said biological polymers are covalently attached to the substrate.

62. The array of claim 34, wherein said biological polymers have a density exceeding 400 different nucleic acids per cm^2.

63. The array of claim 34, wherein said biological polymers have a density exceeding 1000 different nucleic acids per cm^2.

64. The array of claim 34, wherein said biological polymers include nucleic acids.

65. The array of claim 34, wherein said biological polymers include proteins or polypeptides.

66. The array of claim 34, wherein said biological polymers include one of the following: agonists and antagonists for cell membrane receptor, toxins, venoms, viral epitopes, hormones, hormone receptors, enzymes, enzyme substrates, cofactors, drugs, lectins, sugars, oligosaccharides, and monoclonal antibodies.

67. The array of claim 34 wherein said substrate is optically transparent.

68. A method of using a probe array, comprising:

providing an array of probes, comprising biological polymers immobilized on a substrate, having a density exceeding 100 different polymers per cm^2;

providing a bar code associated with said probe array;

reading said bar code;

aligning said probe array with a detection system; and

detecting a signal from said probe array.

69. The method of using a probe array according to claim 68, wherein said nucleic acids have a density exceeding 400 different polymers per cm^2.

70. The method of using a probe array according to claim 68, wherein said polymers have a density exceeding 1000 different nucleic acids per cm^2.

71. The method of using a probe array according to claim 68, wherein said detecting said signal includes detecting a fluorescent signal emitted from said probe array.

72. The method of using a probe array according to claim 68, wherein said detecting said signal comprises scanning said probe array to quantitatively analyze said hybridization between said probes and targets.

73. The method of using a probe array according to claim 68, wherein said providing said probe array includes selectively illuminating said substrate to attach said biological polymers.

74. A method of using a probe array, comprising:

providing a chip comprising a probe array including biological polymers immobilized on a surface and at least some of said polymers hybridized to a target;

providing a housing, including an alignment structure, said housing being constructed to accommodate said chip and a bar code;

reading said bar code;

aligning said housing with a detection system using said alignment structure; and

detecting a signal from said probe array.

75. The method of using a probe array according to claim 74, wherein said chip is optically transparent.

76. The method of using a probe array according to claim 75, wherein said housing is constructed to receive said chip to form a fluid cavity having said probe array located therein.

77. The method of using a probe array according to claim 75, wherein said detecting said signal includes detecting a fluorescent signal emitted from said probe array and transmitted through said chip to a detection system.

78. The method of using a probe array according to claim 74, wherein said housing includes a fluid cavity and said providing said probe array includes hybridizing said probes to said targets by introducing hybridization fluid inside said fluid cavity.

79. The method of using a probe array according to claim 78 further including controlling temperature of said introduced hybridization fluid.

80. The method of using a probe array according to claim 79 further including circulating said hybridization fluid during said hybridization.

81. The method of using a probe array according to claim 74, wherein said nucleic acids have a density exceeding 400 different nucleic acids per cm^2.

82. The method of using a probe array according to claim 74, wherein said nucleic acids have a density exceeding 1000 different nucleic acids per cm^2.

83. The method of using a probe array according to claim 68 or 74, wherein said biological polymers include nucleic acids.

84. The method of using a probe array according to claim 68 or 74, wherein said biological polymers include proteins or polypeptides.

85. The method of using a probe array according to claim 68 or 74, wherein said biological polymers include one of the following: agonists and antagonists for cell membrane receptor, toxins, venoms, viral epitopes, hormones, hormone receptors, enzymes, enzyme substrates, cofactors, drugs, lectins, sugars, oligosaccharides, and monoclonal antibodies.

86. The method of claims 68 or 74 wherein said reading step occurs either before or after either of said aligning and detecting steps.--

REMARKS

In the Specification, Applicants have introduced on page 6, line 19, the above text taken from U.S. Patent 5,143,854, col. 3, lines 6 through 58 and col.15, line 49 through col. 16, line 13. Since U.S. Patent 5,143,854 was incorporated by reference in the present specification, no new matter was entered.

On page 22, lines 10 and 11 Applicants replaced "U.S. Patent Application Ser. No. 08/495,889 (Attorney Docket Number 11509-117)" with U.S. Patent 5,631,734. Furthermore, Applicants inserted the above text that is a brief summary of the disclosure provided in U.S Patent 5,631,734, in col. 3, line 41 through col. 7, line 19. No new matter was entered.

In the above replacement, Applicants corrected a typographical error that occurred when filing the parent U.S. Application 08/485,452 on June 7, 1995. Specifically, the specification incorporates on page 22, lines 10 and 11, U.S. Patent Application Ser. No. 08/495,889 (Attorney Docket Number 11509-117)". That is, the specification listed "US Patent Application Serial No. 08/495,889" instead of "08/195,889" (i.e., number "1" was incorrectly typed as number "4"). There is no doubt that this was only a typographical error since the incorporated application was also identified by "(Attorney Docket Number 11509-117)." As Appendix A, Applicants enclose the Filing receipt of US Patent Application Serial No. 08/195,889, filed on February 10, 1994, which clearly identifies the corresponding Attorney Docket No. 11509-117. Therefore, there is no question that US Patent Application Serial No. 08/195,889 (now U.S. Patent 5,631,734) was incorporated by reference, on June 7, 1995, into the pending specification. Therefore, in summary, on page 22, lines 10 and 11, Applicants only corrected a typographical error and no new matter was entered.

In response to the Office Action of October 12, 2001, Applicants amended claims 28 through 32, 34 and 35 and included new claims 37 through 86. All pending claims are fully supported by the present specification including the patents and applications incorporated by reference. Below are some illustrative passages that show support for the present claims, however, it is noted that there are other portions of the specification that will also support the claims.

For example, claims 28 and 34 are supported by the specification provided on page 9 line 17 through page 10 line 11, and the recited density of biological polymers is provided in U.S. Patent 5,143,854, which was incorporated by reference and parts were now also introduced in the pending specification.

For example, claim 29 is supported by the specification provided on page 6 line 19 through page 7 line 2, page 9 line 17 through page 10 line 11, and page 22 lines 8 through 16.

For example, claims 30 and 32 are supported by the specification provided on page 22 lines 8 through 16, and by U.S. Patent 5,631,734.

For example, claims 31, 33, 35, and 36 are supported by the specification provided on page 22 lines 8 through 16, and various alignment structures are described in connection with different embodiments disclosed in the pending specification, for example, on page 13 line 10 through page 14 line 2.

For example, claim 37 is supported by the specification provided on page 19 line 17 through 3 and various embodiments disclosed in connection with, for example, Figs. 31-36.

For example, claims 38-43 are supported by the specification provided on page 22 lines 8 through 16, and various alignment structures are described in connection with different embodiments disclosed in the pending specification, for example, on page 13 line 10 through page 14 line 2 and the disclosure provided in US Patent 5,631,734 incorporated by reference.

For example, claims 44 through 50 and 54 through 63 are supported by the specification provided in US Patent 5,143,854, portions of which were introduced in the pending specification.

For example, claims 51 through 53 and 64 through 66 are supported by the specification provided on page 5 lines 24 through page 6 line 8.

For example, claim 68 is supported by the specification provided on page 9 lines 8 through 30, and various alignment structures described in connection with different embodiments disclosed in the pending specification, and the array density described in US Patent 5,143,854, parts of which were introduced into the pending specification.

For example, claim 74 is supported by the specification provided on page 9 lines 8 through 30, and various alignment structures are described in connection with different embodiments disclosed in the pending specification, and the description of a detection system provided on page 22 lines 8 through 16 and in US Patent 5,631,734.

For example, claims 69, 70, 73, 81 and 82 are supported by the specification provided in US Patent 5,143,854, portions of which were introduced into the pending specification.

For example, claims 71, 75, 76, 77 and 86 are supported by the specification provided on page 22 lines 8 through 16, and various alignment structures are described in connection with different embodiments in the pending specification.

For example, claims 83 through 85 are supported by the specification provided on page 5 line 24 through page 6 line 9.

The rejections:

The Examiner objected to the wording of claim 34. Applicants amended claim 34 to overcome this objection.

In the Office Action of October 12, 2001, the Examiner rejected claims 28 through 36 under 35 U.S.C. §103(a) as obvious over U.S. Patent 5,636,612 to Mitsuhashi et al. in view of U.S. Patent 5,538,691 to Clark et al. Applicants respectfully disagree with these rejections if again applied to the above claims.

Mitsuhashi teaches a microtiter plate having a plurality of wells with different polynucleotide probes for hybridization. However, the microtiter plate of Mitsuhashi differs fundamentally from the claimed substrate with immobilized probe arrays located thereon. Furthermore, Mitsuhashi does not teach a housing including a fluid cavity for hybridization, as claimed in several pending claims. Additionally, as acknowledged by the Examiner, Mitsuhashi does not teach or even suggest the use of a bar code.

Clark discloses an automated continuous and random access analytical system having an apparatus and methodology capable of simultaneously performing multiple assays of liquid samples. In col. 27, Clark provides description of Kitting and Process Area Activities FPIA. As part of the process, the system updates consumable inventory files. Specifically, in col. 27, lines 29 through 41, Clark states that "[i]nstrument

automatically scans all reagent packs onboard to verify reagent status. Each reagent pack is positioned in front of the reagent pack barcode reader by rotation of the reagent carousel. Reagent pack barcode reader reads barcode to identify assay type and carousel location. If the barcode is unreadable, the system will request a barcode override. If the barcode is good or override complete, the system will check the system inventory..."

There are fundamental differences between the teaching of Clark, alone or in combination with Mitsuhashi, and the claimed invention. The reagent packs of Clark, of course, cannot be equated with the probe arrays claimed in various pending claims. The present independent claims are directed to a package (or a substrate) including a chip having a probe array and an associated bar code. Furthermore, independent claims 28, 29, 37 and 74 recite a housing designed to accommodate the bar code.

Upon close reading of the pending claims, the Examiner will appreciate the above-mentioned fundamental differences between the teachings of Clark and the present invention claimed in independent claims 28, 29, 34, 37, 68 and 74. Furthermore, Mitsuhashi or Clark provide no teaching or suggestion that would lead a person of ordinary skill in the art to modify their teaching to arrive at the claimed invention.

In summary, independent claims 28, 29, 34, 37, 68 and 74 are patentable over US Patent 5,639,612 to Mitsuhashi in view of US Patent 5,358,691 to Clark. Dependent claims 30 – 33, 35, 36, 38 – 67, 69 – 73, and 75 – 86 include additional novel combinations of elements. Accordingly, all pending claims are in condition for allowance and such action is respectfully requested.

Please apply all charges or credits to the Deposit Account No. 01-0431.

Respectfully submitted,

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CERTIFICATION OF FACSIMILE TRANSMISSION

I hereby certify that the enclosed total of 21 pages including a cover sheet is being facsimile transmitted to the fax number 703-308-4242, in the above-referenced application, to the Patent and Trademark Office on the date shown below.

Typed or Printed Name of Person: Ivan D. Zitkovsky, Reg. No. 37,482 Date: Dec. 20, 2001

Signing Certification

EXHIBIT DD

I hereby certify that this correspondence is being sent by facsimile transmission to: Examiner D. Rees, Ph.D. Fax No.: 1-703-305-7401 Assistant Commissioner for Patents Washington, D.C. 20231, on May 20, 1996

By Christine A. Bybee
Christine A. Bybee

PATENT

Attorney Docket No. 16528X-008200
(client file no. 1091)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

MARK S. CHEE ET AL.

Application No.: 08/327,525

Filed: October 21, 1994

For: COMPUTER-AIDED VISUALIZATION AND ANALYSIS SYSTEM FOR SEQUENCE EVALUATION

Examiner: D. Rees

Art Unit: 1807

AMENDMENT

RECEIVED
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Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

In response to the Office Action mailed December 19, 1995, for which a petition for an extension of time is enclosed, please amend this application as follows.

IN THE CLAIMS:

Please cancel claims ~~1, 3-20~~ and ~~45-59~~ without prejudice. Please add new claims 60-105 as follows.

1-59. --CANCELED--

60. In a computer system, a method of identifying an unknown base in a sample nucleic acid sequence, said method comprising the steps of:

inputting a plurality of probe intensities for a plurality of nucleic acid probes, each probe intensity indicating an extent of hybridization of a nucleic acid probe with at least one nucleic acid sequence including said sample sequence, and each nucleic acid probe differing from each other by a single base;

said computer system comparing said plurality of probe intensities; and

identifying said unknown base according to results of said comparing step.

61. The method of claim 60, wherein said comparing step includes the step of said computer system calculating a ratio of a higher probe intensity to a lower probe intensity.

62. The method of claim 61, wherein said identifying step includes the step of identifying said unknown base according to a nucleic acid probe having said higher probe intensity if said ratio is greater than a predetermined ratio value.

63. The method of claim 62, wherein said predetermined ratio value is approximately 1:2.

64. The method of claim 60, further comprising the step of sorting said plurality of probe intensities before said comparing step.

65. The method of claim 60, wherein said at least one sequence includes a reference sequence.

66. The method of claim 65, wherein said comparing step includes the step of said computer system comparing probe intensities of a probe hybridizing with said sample sequence to said probe hybridizing with said reference sequence.

67. The method of claim 65, wherein said comparing step includes the step of calculating first ratios of a wild-type probe intensity to each probe intensity of probes hybridizing with said reference sequence, wherein said wild-type probe intensity indicates an extent of hybridization of a complementary probe with said reference sequence.

68. The method of claim 67, wherein said comparing step includes the step of calculating second ratios of the highest probe intensity of a probe hybridizing with said sample sequence to each probe intensity of probes hybridizing with said sample sequence.

69. The method of claim 68, wherein said comparing step includes the step of calculating third ratios of said first ratios to said second ratios.

70. The method of claim 69, wherein said identifying step includes the step of identifying said unknown base according to said probe associated with a highest third ratio.

71. The method of claim 68, wherein said comparing step includes the step of calculating a ratio of a highest probe intensity of a probe hybridizing with said reference sequence to a highest intensity of a probe hybridizing with said sample sequence.

72. The method of claim 71, wherein said comparing step includes the step of comparing said ratio to an ~~analogous~~ equivalent ratio of neighboring nucleic acid probes.

73. The method of claim 65, wherein probe intensities of probes hybridizing with said reference sequence are from a plurality of experiments.

74. The method of claim 73, wherein said comparing step includes the step of said computer system comparing probe intensities of probes hybridizing with said sample sequence to statistics about said plurality of experiments.

75. The method of claim 74, wherein said statistics include a mean and standard deviation.

76. The method of claim 73, further comprising the step of normalizing said plurality of probe intensities by dividing each probe intensity by a sum of related probe intensities, wherein related probe intensities are from probes that differ by a single base.

77. The method of claim 60, further comprising the step of subtracting a background intensity from each of said plurality of probe intensities.

78. The method of claim 60, further comprising the step of setting a probe intensity equal to a positive number if said probe intensity is less than or equal to zero.

79. The method of claim 60, further comprising the step of indicating said unknown base is unable to be identified if said plurality of probe intensities have insufficient intensity to identify said unknown base.

80. The method of claim 60, wherein said unknown base is identified as being A, C, G, or T.

81. In a computer system, a method of identifying an unknown base in a sample nucleic acid sequence, said method comprising the steps of:

inputting a plurality of probe intensities for a plurality of nucleic acid probes, each probe intensity indicating an extent of hybridization of a nucleic acid probe with said sample sequence, and each nucleic acid probe differing from each other by a single base;

said computer system calculating a ratio of a higher probe intensity to a lower probe intensity; and

identifying said unknown base according to a nucleic acid probe having said higher probe intensity if said ratio is greater than a predetermined ratio value.

82. The method of claim 81, wherein said predetermined ratio value is approximately 1.2.

83. The method of claim 81, further comprising the step of sorting said plurality of probe intensities before said comparing step.

84. The method of claim 81, further comprising the step of subtracting a background intensity from each of said plurality of probe intensities.

85. The method of claim 81, further comprising the step of setting a probe intensity equal to a positive number if said probe intensity is less than or equal to zero.

86. The method of claim 81, further comprising the step of indicating said unknown base is unable to be identified if said plurality of probe intensities have insufficient intensity to identify said unknown base.

87. The method of claim 81, wherein said unknown base is identified as being A, C, G, or T.

88. In a computer system, a method of identifying an unknown base in a sample nucleic acid sequence, said method comprising the steps of:

inputting a first set of probe intensities, each probe intensity in said first set indicating an extent of hybridization of a nucleic acid probe with a reference nucleic acid sequence, and each nucleic acid probe differing from each other by a single base;

inputting a second set of probe intensities, each probe intensity in said second set indicating an extent of hybridization of a nucleic acid probe with said sample sequence, and each nucleic acid probe differing from each other by a single base;

said computer system comparing at least one of said probe intensities in said first set and at least one of said probe intensities in said second set; and

identifying said unknown base according to results of said comparing step.

89. The method of claim 88, wherein said comparing step includes the step of calculating first ratios of a wild-type probe intensity to each probe intensity of probes hybridizing with said reference sequence, wherein said wild-type probe intensity indicates an extent of hybridization of a complementary probe with said reference sequence.

90. The method of claim 89, wherein said comparing step includes the step of calculating second ratios of the highest probe intensity of probes hybridizing with said sample sequence to each probe intensity of a probe hybridizing with said sample sequence.

91. The method of claim 90, wherein said comparing step further includes the step of calculating third ratios of said first ratios to said second ratios.

92. The method of claim 91, wherein said identifying step includes the step of identifying said unknown base according to said probe associated with a highest third ratio.

93. The method of claim 88, wherein said comparing step includes the step of calculating a ratio of a highest probe intensity in said first set to a highest intensity in said second set.

94. The method of claim 93, wherein said comparing step further includes the step of comparing said ratio to an ~~analogous~~ equivalent ratio of neighboring nucleic acid probes.

95. The method of claim 88, further comprising the step of subtracting a background intensity from each of said plurality of probe intensities.

96. The method of claim 88, further comprising the step of setting a probe intensity equal to a positive number if said probe intensity is less than or equal to zero.

97. The method of claim 88, further comprising the step of indicating said unknown base is unable to be identified if said plurality of probe intensities have insufficient intensity to identify said unknown base.

98. The method of claim 88, wherein said unknown base is identified as being A, C, G, or T.

99. In a computer system, a method of identifying an unknown base in a sample nucleic acid sequence, said method comprising the steps of:

inputting statistics about a plurality of experiments, each of said experiments producing probe intensities, each probe intensity indicating an extent of hybridization of a nucleic acid probe with a reference nucleic acid sequence, and each nucleic acid probe differing from each other by a single base;

inputting a plurality of probe intensities, each probe intensity indicating an extent of hybridization of a nucleic acid probe with said sample sequence, and each nucleic acid probe differing from each other by a single base;

said computer system comparing at least one of said plurality of probe intensities with said statistics; and

identifying said unknown base according to results of said comparing step.

100. The method of claim 99, wherein said statistics include a mean and standard deviation.

101. The method of claim 99, further comprising the step of normalizing said plurality of probe intensities by dividing each probe intensity by a sum of related probe intensities, wherein related probe intensities are from probes that differ by a single base.

102. The method of claim 99, further comprising the step of subtracting a background intensity from each of said plurality of probe intensities.

103. The method of claim 99, further comprising the step of setting a probe intensity equal to a positive number if said probe intensity is less than or equal to zero.

104. The method of claim 99, further comprising the step of indicating said unknown base is unable to be identified if said plurality of probe intensities have insufficient intensity to identify said unknown base.

105. The method of claim 99, wherein said unknown base is identified as being A, C, G, or T.--

REMARKS

Claims 60-105 are pending in the subject application. In a sincere effort to expedite prosecution Applicants canceled claims 1, 3-20 and 45-59. However, Applicants reserve all right to pursue these or other claims in another application. In light of the amendments and following remarks, Applicants believe all claims now pending are in condition for allowance.

Claims 1, 3-20 and 45-59 were rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject invention. Claims 1, 3-20 and 45-59 were rejected under 35 U.S.C. § 103 as being unpatentable over WO 92/10588 by Fodor et al. ("Fodor") in view of U.S. Patent No. 5,470,710, issued November 28, 1995 to Weiss et al. ("Weiss") and U.S. Patent No.

5,273,632, issued December 28, 1993 to Stockham et al. ("Stockham").

Formal Matters

Applicants appreciate the Examiner's time in discussing the subject application in a telephonic interview on May 20, 1996. In the interview, the Examiner stated that the phrase "relative (sic) small" in claim 78 may be indefinite as it is unclear how relatively small is determined. Applicants changed the claim to delete this phrase so the claim recites that the probe intensity will be set to a positive number if the probe intensity is less than or equal to zero. As discussed in the interview, for a number of different reasons, adjusted probe intensities may become negative or zero. Thus, these probe intensities may be set to a positive number (preferably small) to prevent utilizing negative numbers or zero in future calculations (see page 15, lines 23-29). Applicants similarly changed claims 85, 96 and 103 so Applicants believe that these claims are patentably definite.

The Examiner also requested that Applicants discuss U.S. Patent No. 4,965,725, issued October 23, 1990 to Rutenberg et al. ("Rutenberg") and U.S. Patent No. 4,741,043, issued April 26, 1988 to Bacus. Applicants will discuss these references at the end of this Amendment.

In the Office Action, the Examiner rejected claims 1, 3-20 and 45-59 under § 112, second paragraph, and § 103. In order to expedite prosecution, Applicants canceled these claims rendering the rejections moot. Applicants added new claims and the following paragraphs will show how these claims are allowable over the rejections.

Applicants appreciate the Examiner's careful attention to the pending claims. Although claims 1, 3-20 and 45-59 were canceled, the following will briefly describe how the new claims are patentably definite over the § 112 rejections cited in the Office Action. For the Examiner's convenience, Applicants will label the paragraphs according to the labels in the Office Action.

a) In regard to claim 1, the Examiner stated that it is not clear how a probe intensity is associated with a nucleic acid probe. As the Examiner suggested, Applicants amended claim 60 to recite "each probe intensity indicat[es] an extent of hybridization of a nucleic acid probe with at least one nucleic acid sequence including said sample sequence." Accordingly, the rejection does not apply to the new claims.

b,c) Also in regard to claim 1, the Examiner stated that "substantially" and "associated" were indefinite or lack antecedent basis. As claim 60 does not contain these words, the rejection does not apply to the new claims.

d) In regard to claim 1, the Examiner stated that it is unclear how "calling" is defined. Claim 60 recites instead "identifying said unknown base" as was suggested by the Examiner in paragraph e). The Examiner also stated that there seems to a step missing. Applicants do not believe that any steps are missing in claim 60. Accordingly, the rejection does not apply to the new claims.

e) In regard to claim 4, the Examiner stated that the phrase "calling said unknown base as being a base" is unclear. Claim 60 recites instead "identifying said unknown base" as suggested by the Examiner. Additionally, the Examiner stated that it is unclear what a "predetermined ratio value" is. A predetermined ratio value is typically a constant number like 1.2 (see, e.g., claim 63). In the interview, it is believed that the Examiner tentatively agreed that this phrase is patentably definite.

f) In regard to claim 6, the Examiner stated that the "step of sorting" is unclear. Claim 64 recites that a step of sorting probe intensities is done "before said comparing step" (see, e.g., page 14, lines 17-22). Accordingly, the rejection does not apply to the new claims.

g) In regard to claim 9, the Examiner stated that it is unclear how "wild-type" is defined with respect to the "reference sequence." Claim 67 recites that the wild-type probe intensity indicates the extent of hybridization of a complementary probe with the reference sequence. Since the reference sequence is a

known sequence, the wild-type probe is also known (see, e.g., page 20, lines 1-7). Also, the Examiner stated that "each probe intensity of a probe" is unclear. Claim 67 recites instead "each probe intensity of probes" (emphasis supplied). Accordingly, the rejection does not apply to the new claims.

h) In regard to claims 9 and 10, the Examiner stated that the phrases "first ratios" and "second ratios" are not clearly defined. The Examiner suggested that the problem is similar to that of claim 9. As claim 68 recites that "each probe intensity of probes hybridizing with said sample sequence" (emphasis supplied), the rejection does not apply to the new claims.

i) In regard to claim 12, the Examiner stated that the phrase "comparing said ratio of neighboring nucleic acid probes" is unclear. Claim 72 recites instead "comparing said ratio to an analogous ratio of neighboring nucleic acid probes" (emphasis supplied). In the interview, the Examiner stated that she understood what Applicants are claiming and would consider if there is a clearer way to recite this in the claims. Applicants invite the Examiner to contact the undersigned if it would aid in prosecution of the subject application.

j) In regard to claims 13 and 14, the Examiner stated that it is not clear how "a" probe generates more than one intensity. Claims 73 and 74 instead contain the plural "probes." Additionally, the Examiner queried how probe intensities may be compared to statistics. One method described in the specification is to compare the probe intensities to a mean and standard deviation (see also claim 75). As to what the result of the comparison will be, this may depend on the implementation of the invention and the data. Accordingly, the rejection does not apply to the new claims.

k) In regard to claim 16, the Examiner stated that it is not clear what is meant by "related probe intensities." Claim 76 recites that "related probe intensities are from probes that differ by a single base" (see also page 31, lines 14-38). Accordingly, the rejection does not apply to the new claims.

l) In regard to claim 17, the Examiner stated that it is unclear how a background intensity is determined. Applicants respectfully point out that it is not necessary that a claim specifically recite "how" each step may be performed. In general, this is the purpose of the specification. Nevertheless, the Examiner stated that the background intensity may be measured before hybridization of the probes. Additionally, the background intensity may be measured from "blank" probes (see, e.g., page 8, lines 27-31). Accordingly, the rejection does not apply to the new claims.

m-t) same as above

The above has shown that the § 112, second paragraph, rejections in the Office Action do not apply to the pending claims. Therefore, Applicants believe that the claims are patentably definite under § 112.

The Invention

The present invention provides innovative computer-aided methods for identifying unknown bases in nucleic acids. The methods compare probe intensities that indicate the extent of hybridization of a nucleic acid probe with a sample nucleic acid, where each of the nucleic acid probes differ from each other by a single base. After comparing the probe intensities, an unknown base is identified (typically as A, C, G, or T) according to the results of the comparison. In one embodiment, a ratio is calculated between the highest probe intensity and the next highest probe intensity. If the ratio is greater than a predetermined ratio value (e.g., 1.2), the unknown base is identified according to nucleic acid probe that produced the highest probe intensity.

The Cited Art Distinguished

Claims 1, 3-20 and 45-59 were rejected under 35 U.S.C. § 103 as being unpatentable over Fodor in view of Weiss and Stockham. Fodor describes, among other things, pioneering techniques for sequencing by hybridization. However, the Examiner cited Weiss and Stockham for disclosing the base calling

(identifying) methods of the present invention. For the following reasons, these references do not disclose or suggest the present invention as claimed.

Weiss and Stockham are related to nucleic acid sequencing which utilizes nucleic acid ladders which may be formed by well known techniques such as the Sanger dideoxy method or the Maxam and Gilbert method. More specifically, Weiss describes utilizing an enzyme on identical probes that hybridize with tags in the fragments of the nucleic acid ladder. The enzymes convert a fluorogenic substrate (e.g., BBTP) into a fluorescent product in order to enhance the pattern of hybridization (see, e.g., Fig. 1C).

Stockham, more specifically, describes methods of sharpening signal peaks from electrophoretic migration patterns of nucleic acid ladders. Each fragment of the nucleic acid ladder is labeled with a radioactive label which is utilized to identify the position of the fragment on the gel following electrophoresis. As analyzing the migration patterns is time consuming and often error prone, Stockham describes equations and formulas for increasing the accuracy of this process (e.g., sharpening signal peaks).

Weiss and Stockham do not disclose or suggest inputting probe intensities to identify an unknown base where the probe intensities indicate the extent of hybridization of probes differing by a single base and the sample nucleic acid sequence. Claim 60 recites the following:

> inputting a plurality of probe intensities for a plurality of nucleic acid probes, each probe intensity indicating an extent of hybridization of a nucleic acid probe with at least one nucleic acid sequence including said sample sequence, and each nucleic acid probe differing from each other by a single base;

(emphasis supplied). Neither Weiss nor Stockham discloses these limitations.

Initially, Weiss uses a single probe which will hybridize to a tag on the nucleic acid ladder fragments. As such, all of the "probes" in Weiss are identical. Furthermore, the probes in Weiss do not indicate the extent of hybridization but instead are utilized to generate a fluorescent signal which

indicates the location of a fragment on the substrate. Accordingly, it is the location of the fragments that is utilized to sequence a nucleic acid.

Stockham does not utilize probes at all. Instead, Stockham recites that the fragments of the nucleic acid ladder are radioactively labeled. The radioactive signal resulting indicates the position of the fragments on the gel in a way which is similar to Weiss. Accordingly, Stockham also utilizes the location of the fragments to sequence a nucleic acid.

In stark contrast, the present invention compares probe intensities that indicate the extent of hybridization of probes differing by a single base and the sample nucleic acid sequence. Claim 60 recites the following:

> said computer system comparing said plurality of probe intensities; and
> identifying said unknown base according to results of said comparing step.

In the Office Action, the Examiner stated that it would have been prima facie obvious to one of ordinary skill in the art to use the computer algorithms of Weiss and Stockham to interpret that data from the sequencing by hybridization described by Fodor. More specifically, the Examiner stated that one could "call" a site based on the intensity of a signal produced by a probe at that site and thus assign an identity to that site. Applicants disagree.

Weiss and Stockham relate to vastly different technologies than the pioneering advances of Fodor. Weiss and Stockham are directed to identifying the location of a fragment of a nucleic acid ladder. In the present invention, the locations of the hybridized probes are known and, as such, the computer algorithms of Weiss and Stockham would indeed seem to teach away from the present invention which is directed to calling an unknown base according to probe intensities from nucleic acid probes that differ by a single base.

As Weiss and Stockham do not disclose or suggest all the limitations of claim 60, the claim is patentably distinct over the references. All the other pending claims contain similar limitations. Therefore, Applicants request that all the

pending claims be passed to issue.

Other Claims

Independent claims 81, 88 and 99 recite specific methods of identifying unknown bases. Details on specific embodiments of these methods may be found in the specification under the headings "Intensity Ratio Method," "Reference Method" and "Statistical Method." These claims recite methods that are patentable for at least the same reasons as above. Additionally, these claims include further limitations that make them further patentably distinct.

Claim 81 recites that a ratio of a higher probe intensity and a lower probe intensity is calculated. Then, the unknown base is identified according to the probe that had the higher probe intensity if the ratio is greater than a predetermined ratio value. Weiss and Stockham simply do not disclose or suggest this method. Accordingly, claims 81-87 are patentably distinct.

Claim 88 recites that probe intensities from a first set of probe intensities from probes hybridizing with a reference nucleic acid sequence and a second set of probe intensities from probes hybridizing with a sample nucleic acid sequence are compared. Based on this comparison, the unknown base is identified. Weiss and Stockham do not disclose or suggest this method. Accordingly, claims 88-98 are patentably distinct.

Claim 99 recites that a probe intensity of a nucleic acid probe hybridizing with a sample sequence is compared to statistics from nucleic acid probes hybridizing with a reference sequence. Based on this comparison, the unknown base is identified. Weiss and Stockham do not disclose or suggest this method. Accordingly, claims 99-105 are patentably distinct.

Additionally Cited Art

In the Office Action, the Examiner cited Rutenberg and Bacus as relevant to programs designed to distinguish ratios of intensities of light. Although in the interview the Examiner stated that these references may be nonanalogous art, she

requested that these references be discussed by Applicants. The following will show that these references do not teach or suggest the present invention regardless of whether the references are analogous art.

Rutenberg describes a two stage neural network system for classifying cells on a slide, e.g., for detecting cervical cancer. In a first stage, the neural network classifies cells or objects which are pre-malignant and malignant. However, the first stage may include other nonmalignant objects like cell clumps, debris, leucocytes, and mucus. A second stage of the neural network is utilized to distinguish the pre-malignant and malignant cells from the nonmalignant objects. As Rutenberg describes methods of distinguishing objects on a slide utilizing neural networks, the reference does not disclose or suggest the base calling methods of the present invention.

Bacus describes a method for overcoming staining variations among cells for analysis, e.g., for cancer diagnosis and prognosis. Conventional staining mechanisms may have variations among experiments so reference cells are placed on the slides with the specimen cells. After staining, the imaging apparatus is calibrated according to the reference cells. The specimen cells are then analyzed to determine characteristics such as nuclear optical density. As Bacus describes methods of calibrating imaging apparatus for analyzing cells on a slide, the reference does not disclose or suggest the base calling methods of the present invention.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at (415) 326-2400.

Respectfully submitted,

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Atty Docket No. 16528X-008200

PTO FAX NO.: 1-703-305-7401

ATTENTION: EXAMINER D. REES, PH.D., ART UNIT 1807

CERTIFICATION OF FACSIMILE TRANSMISSION

I hereby certify that the following Amendment, in re Application of Mark S. Chee, Application No. 08/327,525, filed October 21, 1994, for COMPUTER-AIDED VISUALIZATION AND ANALYSIS SYSTEM FOR SEQUENCE EVALUATION is being transmitted by facsimile to the Patent and Trademark Office on the date shown below.

Number of pages being transmitted, including this page: 23

Dated: May 20, 1996

Christine A. Bybee

Christine A. Bybee

PLEASE CONFIRM RECEIPT OF THIS PAPER BY RETURN FACSIMILE AT (415) 576-0300

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Atty. Docket No. 165? 008200

Date May 20, 1996

In re application of Mark S. Chee et al.

Appln. No. 08/327,525

Filed October 21, 1994

Group Art Unit 1807
For COMPUTER-AIDED VISUALIZATION AND ANALYSIS SYSTEM FOR SEQUENCE EVALUATION

I hereby certify that this correspondence is being sent by facsimile transmission to: Examiner D. Rees, Ph.D.
Fax No.: 1-703-305-7401
Assistant Commissioner for Patents,
Washington, D.C. 20231
on: May 20, 1996

by: Christine A. Bybee
Christine A. Bybee

THE ASSISTANT COMMISSIONER FOR PATENTS
Washington, D.C. 20231

Sir:

Transmitted herewith is an amendment in the above-identified application.

[X] Enclosed is a petition to extend time to respond.
If any extension of time is needed, then this response should be considered a petition therefor.
The filing fee has been calculated as shown below:

	(Col. 1) CLAIMS REMAINING AFTER AMENDMENT		(Col. 2) HIGHEST NO. PREVIOUSLY PAID FOR	(Col. 3) PRESENT EXTRA	SMALL ENTITY RATE	SMALL ENTITY ADDIT. FEE	OR	OTHER THAN A SMALL ENTITY RATE	OTHER THAN A SMALL ENTITY ADDIT. FEE
TOTAL	*46	MINUS	**44	=2	x11=	$		x22=	$44
INDEP.	*4	MINUS	***3	=1	x39=	$		x78=	$78
[ ] FIRST PRESENTATION OF MULTIPLE DEP. CLAIM					+125=	$		+250=	$
					TOTAL ADDIT. FEE	$	OR	TOTAL	$122

* If the entry in Col. 1 is less than the entry in Col. 2, write "0" in Col. 3.

** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, write "20" in this space.

*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, write "3" in this space.
The "Highest Number Previously Paid For" (Total or Independent) is the highest number found from the equivalent box in Col. 1 of a prior amendment or the number of claims originally filed.

[ ] No fee is due.

Please charge Deposit Account No. 20-1430 as follows:

[X] Claims fee $122

[X] Any additional fees associated with this paper or during the pendency of this application.

2 extra copies of this sheet are enclosed.

TOWNSEND and TOWNSEND and CREW LLP

Michael J. Ritter
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